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**Does Daily Intake of Glucosamine Supplements Prevent the
Need for Knee Replacements Later in Life for Adult Patients
Predisposed to Osteoarthritis?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE:

The objective of this selective EBM review is to determine whether or not daily intake of glucosamine supplements prevents the need for knee replacements later in life for adults predisposed to osteoarthritis.

STUDY DESIGN:

Review of three English language primary randomized controlled trial studies published between 2001 and 2008

DATA SOURCES:

Three double blind randomized control trials comparing glucosamine supplements to placebo were found using PubMed.

OUTCOMES MEASURED:

Outcomes were measured using radiographic studies of the knees, joint space measurements, and symptoms were evaluated using Lequesne and WOMAC indexes.

RESULTS:

The Reginster (2001) and Pavelka (2002) studies demonstrated no change in joint space measurements in the experimental glucosamine group and a 20-25% decrease in symptoms such as pain and stiffness in the Pavelka study. In the Bruyere (2008) study, 19 out of 131 (14.5%) of those in the placebo group underwent total joint replacement five years after the trial and 9 out of 144 (6.3%) of those in the experimental glucosamine group underwent total joint replacement five years after the trial.

CONCLUSIONS:

The three randomized controlled trial in this review concluded that glucosamine supplements retard the progression of joint space narrowing and will delay the need for a total joint replacement up to five years after discontinuing glucosamine supplements.

KEY WORDS:

Glucosamine, Osteoarthritis, joint space narrowing, total joint replacements

Introduction

Knee Osteoarthritis (OA) is the most common form of osteoarthritis and fifth leading cause of disability in the United States¹. The only cure for knee OA is total joint replacement (TJR). Knee osteoarthritis is conventionally managed symptomatically using anti-inflammatory medication such as naproxen and over-the-counter (OTC) pain medications. Unlike Rheumatoid arthritis, there is not a disease modifying medication, like the DMARD class of medication, for osteoarthritis. Thus, healthcare providers are treating the symptoms without slowing the progression of cartilage breakdown. As the patient's function deteriorates further, symptomatic treatment becomes ineffective and TJR is warranted. Glucosamine supplements have been advertised as OTC supplements for alleviating joint pain and promoting joint health. Research has shown that glucosamine supplements have the potential of slowing down the progression of joint space narrowing when compared to placebo while improving OA symptoms and restoring function.

The use of glucosamine supplements in the management of OA is relevant to patients and the physician assistant (PA) practice because managing OA can be a financial burden on the patient and the loss of function can be life changing. Approximately 27 million Americans suffer from OA¹. In the western world, 5-15% of people 35-74 years of age will have radiographic changes on knee studies such as joint space narrowing². Since OA is common, the cost of management and treatment is a burden on society. In 2007, the cost for arthritis was \$128 billion per year in medical care and indirect expenses such as lost wages³. As of 2004, the total annual cost of OA per person was estimated to be \$5700³. As for the number of visits per year, in 1993, it

was estimated that an OA patient schedules 3.3 office visits per year¹. Current data is unavailable due to the type of management the patient is seeking (such as injections, post-op, etc).

Osteoarthritis is a degenerative progressive condition characterized by joint pain, joint stiffness after activities, as well as osteophyte formation seen on radiographic studies. It also includes the breakdown of cartilage in the joints which causes the symptoms mentioned above. The exact cause of osteoarthritis is unknown and therefore thought to be idiopathic. However, it is associated with obesity, repetitive motion, injuries, and aging.

As mentioned above, OA is treated symptomatically with analgesics such as Tylenol. Synovial joint injections are also used lubricate the knee and prevent the “bone-on-bone” rubbing due to cartilage loss. Physical and occupational therapy as well as weight reduction are also implemented in the management of OA³.

Currently, TJR is the definitive cure for knee arthritis. Not all of those affected by OA are eligible for TJR. In general, the surgeon considers the patient’s health, severity of the symptoms, extent of the disability, as well as age. Surgeons are less likely to perform TJR on a younger person, less than 65 years old, due to the life-expectancy of the prosthetic components—a younger person will more likely have to undergo a revision surgery later on in life to replace worn out prosthetic components. The revision surgery is more difficult than TJR and carries more risks and complications as well. Therefore, a supplement with disease retarding capability will benefit the patients and reduce the number of procedures they may undergo in their lifetime. Glucosamine sulfate has been

shown to slow down the progression of knee arthritis and preserving the joint space. Since the joint space is maintained, the patients' symptoms lessen in severity or even cease. Thus restoring function and productivity as well as delaying the need for a surgical intervention such as a total joint replacement. This eliminates the financial burden of having multiple surgical interventions and improving the patients' quality of life.

Objective:

The objective of this selective EBM review is to determine whether or not daily intake of glucosamine supplements prevents the need for knee replacements later in life of adults predisposed to osteoarthritis.

Methods:

Studies were selected based on population and type of intervention. The studies selected focused on adults over 18 years of age with OA symptoms. The intervention was oral glucosamine supplements. The studies compared the treatment group which received 1500mg of oral glucosamine supplements daily and the control group which received a placebo daily. The outcomes were measured using radiographic imaging to measure the joint space. The tibiofemoral joint space was measured and compared to the measurement taken prior to the start of the trial. Symptoms were assessed using algofunctional indexes of Lequesne and WOMAC. All three studies were randomized placebo controlled trials.

A detailed search using PubMed and EBSCOhost was conducted using glucosamine supplements and knee osteoarthritis as keywords. All of the articles found and used in this review were published in peer-reviewed journals and written in English

between 2001 and 2008. The author of this review conducted the research and selected the studies based on the relevance and on the importance of outcomes to the patients (POEMS). The inclusion criteria were randomized controlled double blind studies performed after 1996 using glucosamine as an intervention. The exclusion criteria were patients over the age of 18, patients with hip arthritis, and using chondroitin as an intervention. The statistics reported and used were 95% confidence intervals, numbers-needed to harm (NNH), and p-values.

Table 1: Demographics and characteristics of included studies

Study	Type	# pt	Age	Inclusion criteria	Exclusion criteria	W/D	Intervention
Pavelka ¹ (2002)	Double blind RCT	202	45- 70	Primary knee OA -diagnoses based on clinical and radiological criteria of the American College of Rheumatology -minimum score of 4 on Lequesne index	-Lequesne score of 12 - history of articular and rheumatic diseases other than OA - history of traumas or lesions of the knee -severe articular inflammation - rapidly progressive osteoarthritis -overweight (BMI >27). - systemic or intra-articular corticosteroid use 3 months prior to trial.	81	1500mg glucosamine sulfate PO QD x 3 years
Reginster ⁴ (2001)	Double blind RCT	212	>50	Primary knee OA and over age 50	-history or active presence of	73	1500mg glucosamine sulfate PO

					other rheumatic diseases -severe articular inflammation -traumatic knee lesions -overweight (BMI >30) -intra-articular or systemic corticosteroids in the 3 months prior to trial		QD x 3 years
Bruyere ⁵ (2008)	Double blind RCT	275	40- 70	Participation in 3 year trial in the past	Had TKR surgery after pervious trial	0	Followed for incidence of TJR

Outcomes measured:

The outcomes measured were patient oriented evidence that matters (POEMs). The objective data was measured using radiographic studies. The radiographic studies were conducted at the time of enrollment, after one year of treatment, and after 3 years of treatment. The medial joint space of the knee was then measured. To assess the symptoms, the Reginster et. al study used WOMAC while the Pavelka et. al used Lequesne and WOMAC. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is used to assess the severity of arthritis related symptoms such as pain (score from 0-20), stiffness (score 0-8), and function limitations (score 0-68)⁴. The Lequesne Algo-functional index measures pain, distance walked, and activities of daily living⁵.

Results:

In Pavelka, et. al, there was progressive joint space loss in the placebo group while there was no progression in joint space narrowing in the glucosamine group. At the end of the 3 year trial, there was 0.36mm difference in joint space between the two groups with 95% confidence interval of 0.13-0.59mm and a p-value <0.001.²

Table 2: Intent-to-Treat Cumulative Joint Space Narrowing (in mm) at Each Year of Treatment

Year	Placebo	Glucosamine	Difference	p-Value
1	-0.04	-0.05	0.097	0.049
2	-0.08	-0.03	0.11	0.030
3	-0.19	-0.04	0.23	0.001

As for the symptoms, the glucosamine group had a 20%-25% score reduction on the WOMAC and Lequesne indexes with p-value of 0.02 for WOMAC and <0.001 for Lequesne. In addition, the joint stiffness subscale of the WOMAC had a significant reduction in the glucosamine group with -0.31 95% confidence interval (CI) compared to the placebo group which had 0.11 95% CI.² The authors of the study included adverse events reported by the patients during the three year trial. 66% of the placebo group and 64% of the glucosamine group reported at least one adverse event over the course of the three years². The authors did not report significant differences between the groups and the adverse events reported.

Table 3: Adverse Events reported by participants during the course of the trial²

System Organ Class	Placebo	Glucosamine
Gastrointestinal tract and liver	28	25
Musculoskeletal	22	30
Cardiovascular	20	23
Skin and appendages	15	10
Respiratory tract	7	17
Urinary tract	11	12
Metabolic and nutritional	6	7
Other*	14	14

* Isolated adverse events : nervous, psychiatric, blood cell disorders, neoplasms, endocrine disorders, reproductive (male/female), vision disorders, hearing, and vestibular. ²

In Reginster et. al. study, the intention-to-treat analysis showed a lower mean joint space narrowing in the glucosamine group compared to the placebo group. The mean joint space narrowing for the glucosamine group was -0.06mm while the placebo group was -0.31mm with a 95% CI of 0.24 (0.01-0.08) and p-value of 0.043 ⁶. As for the symptoms, the WOMAC index shows worsening of symptoms in the placebo group by the end of the three year trial when compared to the glucosamine group. The difference between the final group averages at the end of the three year period was significant (p=0.016) ⁶. In addition, the study reports an improvement of function and pain on the WOMAC subscales in the glucosamine group. The authors of the study noted that there was improvement of symptoms in the glucosamine group even when the joint space narrowing was considered severe. With regards to adverse events, most of the participants reported at least one adverse event, 93% in the placebo group and 94% in the glucosamine group. The authors did not report any differences between the groups with regards to frequency of events or type of event ⁶. The table below is a summary of the events reported by the participants.

Table 5: Adverse events reported during Reginster et al trial ⁶

Adverse Event	Placebo	Glucosamine
Abdominal pain	18	13
Dyspepsia	8	4
Diarrhea	11	10
Increased blood pressure	15	15
Decreased blood pressure	8	2
Cardiac failure	7	4
Fatigue	7	10
Headache	4	6
Vertigo	3	7
Neuritis	6	4
Depressive mood	7	4
Allergic episode	7	4

In Bruyere et al study, 19 out of 131 (14.5%) placebo recipients underwent a total joint replacement surgery within the 5 years following the end of the trial. Only 9 out of 144 (6.3%) glucosamine recipients underwent TJR after the trial. In other words, twice as many participants in the placebo group underwent TJR compared to the glucosamine group. The study reported a p-value of 0.024 and relative risk of undergoing TJR of 0.43 (95% CI from 0.20 to 0.92) for the glucosamine group participants—a 57% decrease compared to the placebo group. The reported NNT to avoid TJR was 12⁷. With regards to adverse events, the authors did not report adverse events during the course of the trial.

Discussion:

The use of glucosamine sulfate supplements as a daily supplement for an extended period of time has proven effective in delaying the progression of Osteoarthritis and thus the need to undergo total joint replacement surgeries. Glucosamine sulfate supplements are readily available over-the-counter in pharmacies, supermarkets, and health stores such as GNC. After conducting an online price search, the prices of glucosamine sulfate supplements ranged from \$9 to \$35. It is considered a relatively safe supplement with minimal adverse reactions, such as constipation, diarrhea, nausea, vomiting, and pruritus⁸. There are no contraindications for glucosamine⁸. Most of the studies performed up to this date investigated the effects of glucosamine on patients with OA. However, there are studies looking at the effects of the compound on weight loss, glaucoma, multiple sclerosis, and cancer⁸. Other uses for glucosamine have not been studied as extensively as the use for OA.

Some drug interactions were reported for glucosamine sulfate. There is a major interaction warning for the use of glucosamine with Coumadin⁹. There has been several reports of glucosamine increasing the effect of Coumadin thus causing easy bruising and increasing the risk for serious bleeds. There may be a moderate interaction between antimitotic chemotherapy and glucosamine. There is a chance that glucosamine may increase the rate of cell division which may decrease the effectiveness of cancer medications intended to reduce the rate of cell division in tumors⁹. In addition, glucosamine may increase blood sugar levels in diabetics and may decrease the effectiveness of diabetic medications^{8,9}. Glucosamine is not contraindicated in diabetics but diabetic patients are advised to monitor their blood sugar levels more cautiously when taking glucosamine supplements.

The three studies were not limited with regard to sample size and duration of the trial. However, more studies are necessary to adequately conclude that glucosamine supplements may have disease-modifying effects on patients with Osteoarthritis. In addition, the studies should mention the source of glucosamine used in the trial. Since glucosamine is a supplement, it is not FDA monitored and the purity of the OTC supplement should be questioned. There have been reports in the media of OTC supplements with compounds not listed on the bottle which caused adverse events in the users.

Conclusion:

All three studies have shown that glucosamine did retard the progression of osteoarthritis in adults with knee arthritis and did delay the need for total joint

replacement when compared to the placebo group. In addition, those who received glucosamine reported improvement of OA symptoms such as improved function and decrease in pain. Future studies are warranted to evaluate the effects of glucosamine sulfate on young athletes, such as runners and basketball players, who tend to develop OA symptoms at a young age. The study would include athletes between the ages of 18 and 25 with mild knee pain or previous knee injuries which predispose them to OA. It would be interesting to see if glucosamine supplements will halt the progression of joint space narrowing and improve joint function in such active subjects.

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